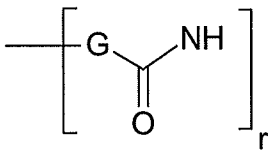
REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

In the Official Action, Claims 1, 3, 5, 6, 9, 11, 13, 14, 24, 26 and 28-34 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. In addition, claims 1, 3, 5, 9, 11, 13, 14, 24, 26 and 28-34 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Finally, claims 1-3, 5-9, 11, 13-15 and 24-30 are rejected are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly obvious over Cozzi et al.(WO 98/04525) in view of Cortes et al. *Investigational New Drugs* 18: 57-82, 2000 ("Cortes").

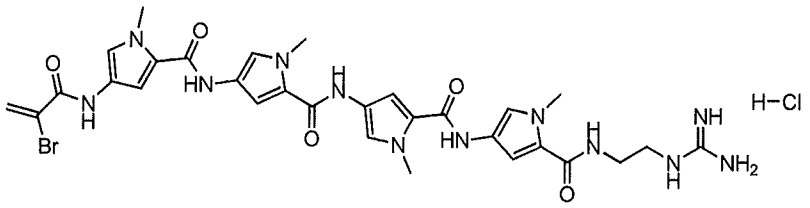
Before addressing the merits, applicants wish to thank Examiner Webb for granting an interview after the issuance of a final rejection and for the courtesy exhibited to their representative at the interview. Applicants also wish to thank Examiner Webb for his helpful suggestions. At the interview, Examiner Webb provided his rationale for the rejections. During the interview, applicants' attorney described various amendments to the claims and Examiner Webb seemed favorably disposed toward same. However, no formal agreement was reached.

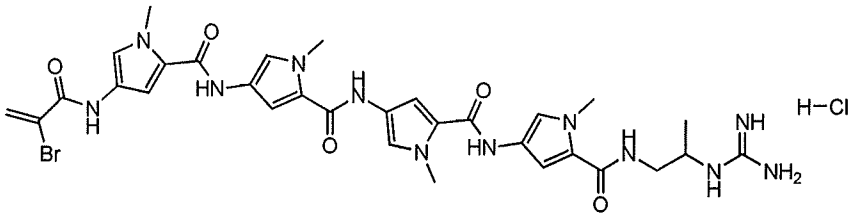
Applicants have amended the claims to recite the language that Examiner Webb appeared to be favorably disposed. Specifically, claim 1 has been amended to define m as 0 or 1, n as 3 or 4, and r as 0, which definitions are within the scope of the original Markush group. It is

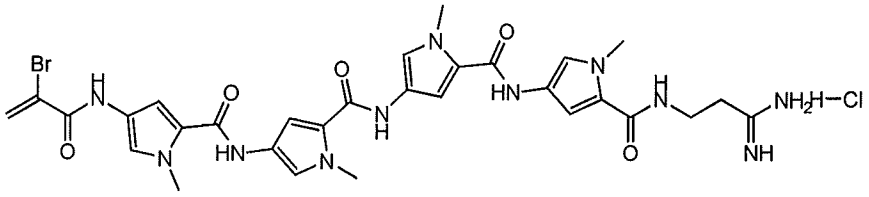


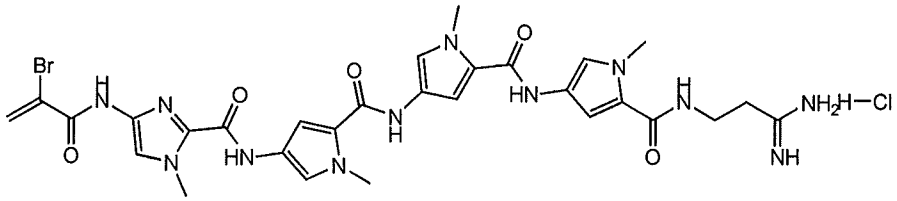
to be noted that when r is 0, is a bond. In addition, applicants have limited the protein kinase inhibitor to ST-1571 and OSI-774 which is within the original Markush group.

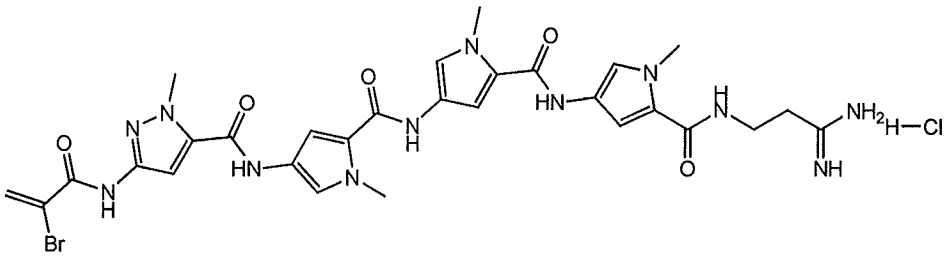
Applicants have amended the claimed subject matter to be closer in structure to that which is exemplified. More specifically, for the convenience of the USPTO, we have drawn the structure of the ten compounds listed on pages 6 and 7 of the instant specification.

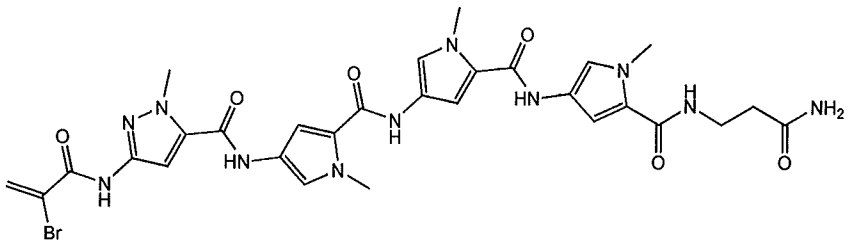


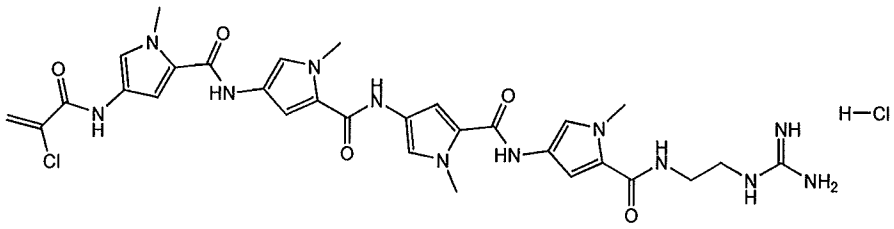


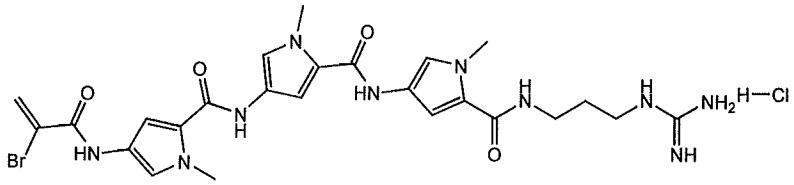


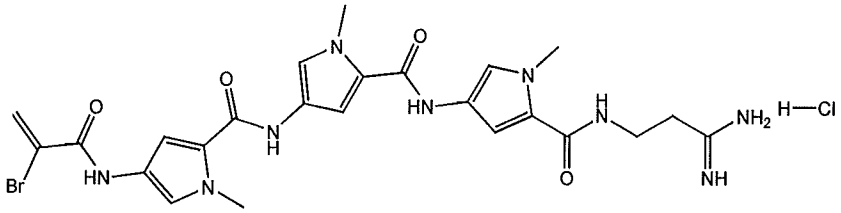


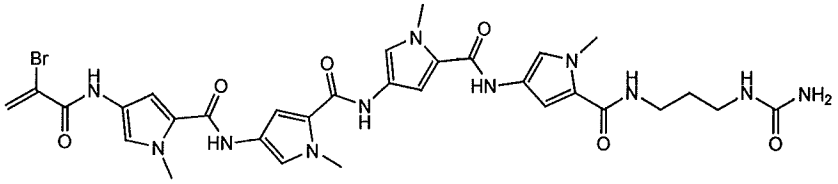












In these species, the specification has exemplified

R_1 is a bromine or chlorine atom;

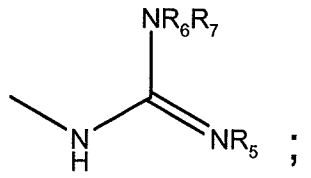
m is 0 or 1;

n is 3 or 4;

r is 0;

X and Y are, the same or different and independently for each heterocyclic ring, a CH group;

B is:



;

R_4, R_5, R_6 and R_7 are hydrogen.

Applicants have narrowed these claims by deleting definitions in the Markush group so that the claims are closer in structure to the exemplification in the application. Further, case law has held that mention of representative compounds may provide an implicit description upon which to base generic claim language. See, In re Robins, 429 F2d 452, 166 USPQ 552, (CCPA 1970).

The claims have also been amended to recite the specific tumors. These are recited on page 10, lines 1-3 of the instant specification.

No new matter has been added to the instant specification.

Pursuant to the rejection of the claims under 35 U.S.C. §103, the Office Action cites Cozzi et al. in view of Cortes.

Specifically, the Office Action contends that Cozzi et al. disclose the acryloyl distamycin derivative of formula I and Cozzi et al. disclose that the acryloyl distamycin derivatives can be combined with an additional antitumor agent for treating cancer or for ameliorating the conditions of mammals, including humans, suffering from cancer. Further, the Office Action admits that Cozzi et al. do not teach any protein kinase inhibitors. However, the Office Action contends that Cortes et al., the secondary reference, teach that CGP 57148 (ST1571) is a novel agent that inhibits the tyrosine kinase activity of ABL, and that clinical results suggest a very potent anti-leukemia activity with minimal toxicity in patients with Interferon-resistant Ph-positive CML. Further, the Office Action contends that, generally, it is

prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. Thus, the Office Action asserts that combining the acryloyl distamycin compounds of Cozzi et al. with the ST1571 of Cortes et al. would achieve the compositions and methods of the present invention since they are both taught to be useful for treating leukemia.

Neither Cozzi et al. nor Cortes et al. teach, disclose or suggest the synergistic effect claimed. As evidence of the synergistic effect, reference is made to the in vitro data in Exhibit 1 submitted on November 7, 2007. The study showed, using representative protein kinase inhibitors and compounds of formula I, that there is a synergistic effect.

The Office Action acknowledges the data presented in Exhibit 1.

In connection with the *in vitro* biological data submitted to the Examiner as "Exhibit 1" in applicants' response dated November 7, 2007, which shows the synergistic effect (i.e. more than additive effect) of the presently claimed composition, it appears that the Office Action recognizes the synergistic effect of the presently claimed composition, but indicates that the claimed subject matter is not commensurate in scope with the showing.

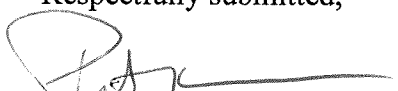
But, contrary to the allegations in the Office Action, the claims are commensurate in scope of the showing. The compounds of formula I and the protein kinase inhibitors recited in the claims encompass the compounds tested. The combinations are, respectively, the combination of brostallicin (an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I)) with ST1571 (a protein kinase inhibitor) on K562 human CML cell lines (leukemia); the combination of brostallicin with ZD1839 (a protein kinase inhibitor) on human lung cancer NCI-H322M human lung cancer cell line, and the combination of brostallicin with OSI-774 (a protein kinase inhibitor) on MDA-MB-468 human breast carcinoma cell line. The *in vitro* data

shows that, on human tumor cells, brostallicin can be combined effectively with each of the above-identified three protein kinase inhibitors to produce a synergistic effect (i.e. more than additive effect). The protein kinase inhibitors are OSI-774 and ST-1571 which are in the showing. Further, the claimed compounds of formula I are commensurate in scope with the compounds utilized in the showing. The rings in R_2 are pyrrolyl, with X + Y being as defined, while B contains imino moieties. In view of the above remarks, applicants submit that the claims, as presently amended, are not obvious over the applied references because the applied references, either alone or in combination, do not teach or suggest that the presently claimed composition, product or method exhibit an antitumor effect or that the antitumor effect of the combination of the protein kinase inhibitor and the compound of Formula I is greater than the additive antitumor effect of the acryloyl distamycin derivative and the protein kinase inhibitor, as shown by the data presented in Exhibit 1, which was submitted concomitantly with applicants' response to Office Action dated November 7, 2007.

In view of the above remarks, applicants submit that this rejection under 35 U.S.C. §103(a) has been obviated. As such, reconsideration and withdrawal of the instant rejection is respectfully requested.

In view of foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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